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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/991,212	11/16/2001	Preeti Lal	PF-0221-3 DIV	9736

27904 7590 03/21/2003

INCYTE GENOMICS, INC.
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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/991,212	LAL ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-7,9,10,12-16,28,29,46-48 and 57-59* is/are pending in the application.

4a) Of the above claim(s) *14-16,28,29,47 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-7,9,10,12,13,46,48,57 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

[1] Claims 3-7, 9, 10, 12-16, 28, 29, 46-48, and 57-59 are pending in the application.

[2] Applicants' cancellation of claim 1, amendment to claims 3, 10, 12, 13, 48, 57, and 58, and addition of claim 59 in Paper No. 7, filed 10/23/02, is acknowledged.

[3] Newly submitted claim 59 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the nucleic acid of SEQ ID NO:5 is *not* a fragment of SEQ ID NO:1 (see attached sequence comparison) as the attached sequence comparison indicates that SEQ ID NO:5 is *not* identical to nucleotides 1183-1454 of SEQ ID NO:1 as stated by applicants in Paper No. 7 (see page 36, lines 14-16). The nucleotide sequence of SEQ ID NO:5 is distinct from SEQ ID NO:1 and thus, examination of claim 59 would require a separate search. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 59 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

[4] Claims 14-16, 28, 29, 47, and 59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

[5] Claims 3-7, 9, 10, 12, 13, 46, 48, 57, and 58 are being examined on the merits.

[6] Applicants' arguments as presented in Paper No. 7 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[7] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

[8] The rejection of claims 3-7, 9 10, 12, 13, 46, 48, 57, and 58 under 35 U.S.C. 101 is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous

Office action (see item 4 of Paper No. 6). Applicants' arguments are summarized and rebutted as follows. For applicants' convenience, the examiner's rebuttal of applicants' arguments will maintain the format as used by applicants in Paper No. 7.

Beginning at page 9 of Paper No. 7, applicants characterize the invention as a polynucleotide sequence corresponding to a gene that is expressed in human brain tumor tissues and encodes a polypeptide, which is a member of the phosphate transporter family having biological functions including regulation of intracellular phosphate levels. Applicants assert the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development and diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the claimed polynucleotide actually functions. Applicants assert the claimed invention already enjoys significant commercial success. Applicants' arguments are not found persuasive. It is noted that, while the nucleic acid is asserted to have been identified from a sample of human brain tumor tissue, there is no indication in the specification that this nucleic acid is expressed only in tumor or brain tumor tissue, nor is there indication that this nucleic acid has altered expression in tumor or brain tumor tissue as compared to normal tissue. Absent such a disclosure of altered levels or forms of a gene in diseased tissue as compared with the corresponding normal, i.e., healthy, tissue, the gene is not a disease marker or an appropriate target for drug discovery or toxicology testing. Finally, evidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is immaterial to utility and enablement. Many products have enjoyed commercial success due to fads or clever advertising, wherein the products would not have met the legal standards for utility and enablement.

Beginning at page 9, second paragraph of Paper No. 7, applicants discuss the Bedilion declaration (cited by applicants) submitted with Paper No. 7. Applicants characterize the Bedilion declaration as describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications, thus allegedly demonstrating the examiner's position to be without merit. In particular, applicants state the Bedilion declaration describes how the claimed polynucleotide can be used in gene expression monitoring systems that were well known at the time of the invention, and how those

applications are useful in developing drugs and monitoring their activity. Applicants quote from the Bedilion declaration, that states in summary that a cDNA microarray containing a SEQ ID NO:1-encoding polynucleotide would be a more useful tool than a cDNA microarray lacking same in connection with conducting gene expression monitoring studies on proposed or actual drugs for treating disorders associated with increased or decreased phosphate levels for such purposes as evaluating their efficacy and toxicity. Applicants' argument is not found persuasive. It is noted that Dr. Bedilion is a consultant for Incyte Pharmaceuticals, Inc., and thus is a concerned party. Regarding the merit of the examiner's position, *any* polynucleotide can be used in a microarray, just as any polynucleotide can be used for expression of an encoded protein or as a hybridization probe. Thus, this asserted utility is *not* specific. Also, the disclosure appears to assert that, because NAPTR (SEQ ID NO:1) has 48 % identity to human renal sodium phosphate transport protein (NPT1) and 29 % identity to rat brain-specific sodium-dependent inorganic phosphate cotransporter (rBNPI) at the amino acid level, NAPTR (SEQ ID NO:1) functions as a sodium phosphate transport protein. However, it is well known in the art that sequences sharing identity do not necessarily share function. Furthermore, because NAPTR (SEQ ID NO:1) and NPT1 share identity at the amino acid level does not render the asserted utility specific, since the specification does not establish that NAPTR (SEQ ID NO:1) is expressed in any diseased tissues in a form or level that is different from a form or level of the protein expressed in normal tissues. Thus, there is no clear indication that NAPTR (SEQ ID NO:1) is a target for drug development, toxicology studies, or disease diagnosis for (quoting from the Bedilion Declaration) "disorders associated with increased or decreased phosphate levels". As such, additional research is required in order to ascertain the function of the encoded protein and to identify a potential disease state or states which correlate with altered levels or forms of the claimed polynucleotide. Therefore, this asserted utility is also not substantial.

Beginning at the bottom of page 9 of Paper No. 7, applicants argue the Office action does not dispute that the claimed polynucleotides can be used as probes in cDNA microarrays and used in gene expression monitoring. Applicants argue the examiner's position is the claimed polynucleotide cannot be useful without precise knowledge of its biological function. Applicants argue the law does not require

knowledge of biological function to prove utility. Applicants argue it is the claimed invention's use(s) that are subject to analysis of the utility requirement. The examiner agrees with applicants' argument to the extent that the claimed polynucleotide can be used as a probe in gene expression monitoring. As one of ordinary skill in the art would recognize, any nucleic acid can be used as a probe – this utility is not specific to a particular nucleic acid. The examiner further agrees with applicants' argument to the extent that the utility requirement of 35 USC 101 does not require knowledge of biological function to prove utility. A claimed polynucleotide can meet the legal requirements of utility and enablement as long as the specification discloses a credible, specific and substantial asserted utility or a well-established utility for the claimed polynucleotide. For example, Shattuck-Eidens et al. (US Patent 5,693,473) teach mutant alleles of the *BRCA1* gene that predispose a patient to developing breast and ovarian cancers (abstract). While there is no disclosure of the function of the mutant *BRCA1* genes or their gene products, the invention nevertheless has utility as being an indicator for susceptibility to developing breast and ovarian cancers. Contrary to this example, the instant specification discloses that the claimed polynucleotide encodes a polypeptide that is structurally related to other sodium phosphate transport proteins and predicts that the claimed polynucleotide is involved in disorders associated with phosphate transport. However, there is no indication that the claimed polynucleotide is differentially expressed or is expressed in an altered form in diseased tissues relative to normal tissues. The specification does not disclose any evidence indicating altered forms or expression levels of the claimed polynucleotide in diseased tissue. Also, no evidence has been presented to verify the claimed polynucleotide encodes a polypeptide having sodium phosphate transport activity.

Beginning at the first full paragraph of page 10 Paper No. 7, applicants argue that beneficial results can be achieved from the claimed polynucleotide in the absence of any knowledge as to the function of the encoded protein and assert that the use of the claimed polynucleotide in gene expression monitoring applications are in fact independent of their precise biological function. Applicants argue all polynucleotides expressed in humans have utility in toxicology testing and that this utility is dependent on the identity of the polynucleotide and not on its function or association to a disease state. Applicants

argue the results obtained using an array to detect an expressed polynucleotide is specific to the compound being tested and the detected polynucleotide and therefore, there is no need to link a disease state to the claimed polynucleotide. Applicants argue that, at the very least, an array comprising the claimed polynucleotide can be used as a specific control for toxicology tests. Applicants' arguments are not found persuasive. As stated above, the examiner agrees with applicants' argument to the extent that the utility requirement of 35 USC 101 does not require knowledge of biological function to prove utility. It is evident from the example of Shattuck-Eidens et al. that utility for a polynucleotide does not require knowledge of function. Applicants' line of argument that all polynucleotides expressed in humans have utility in toxicology testing would appear to support the examiner's argument that the claimed polynucleotide has no *specific* utility. If any polynucleotide expressed in a human has utility in toxicology testing, then that polynucleotide has no *specific* utility as all polynucleotides would have such use. Therefore, any human polynucleotide could be used as a control in toxicology testing and thus this use would not be a *specific* utility. If a specific disease state were correlated with the presence of altered levels or form of a given polynucleotide, then that polynucleotide would have *specific* utility as an indicator of disease. Similarly, **all polynucleotides have use for protein expression and the encoded amino acid sequence would be specific and dependent upon the nucleotide sequence of the encoding nucleic acid. However, as all nucleic acids have utility for protein expression, this utility is not specific.**

Furthermore, based on the Bedilion Declaration, one of ordinary skill in the art would recognize that knowledge of the function of the protein encoded by the claimed polynucleotide is necessary to be useful for gene expression monitoring in toxicology, even though such use is non-specific. The Bedilion Declaration states, "a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain any of these polynucleotides, **in connecti n with c nducting gene expression m nitoring studies n... ...drugs f r *disorders associated with increased or decreased phosphate levels for such purposes as evaluating their efficacy and toxicity*** (emphasis added; Bedilion Declaration, paragraph 15). Thus, *it would*

appear from the Bedillion declaration that the function of the polypeptide of SEQ ID NO:1 is indeed required for evaluating drugs associated with increased or decreased phosphate levels.

I. The Applicable Legal Standard

Beginning at page 11 of Paper No. 7, applicants cite case law that is allegedly relevant to the instant rejection. The essential disagreement between the examiner's position and applicants' position appears to be the interpretation of what constitutes a specific, substantial and credible utility, as will be explained in detail below.

II. Toxicology testing, drug discovery, and disease diagnosis are allegedly sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph.

Applicants argue the claimed invention meets the necessary requirements for establishing a credible utility under the law as applicants allege there are "well-established" uses for the claimed invention known to persons of ordinary skill in the art and there are allegedly specific practical and beneficial uses disclosed in the specification for the claimed invention. Applicants argue these uses are explained in the Bedilion declaration and that objective evidence, allegedly not considered by the Office, further corroborates the credibility of the asserted utilities. Applicants' arguments are not found persuasive. The claimed invention has no well-established use and there is no specific, substantial and credible use for the claimed invention, even after full consideration of the "evidence" as provided in the specification. Each of these arguments will be described in more detail below.

A. The use of the claimed polynucleotides for toxicology testing, drug discovery, and disease diagnosis are allegedly practical uses that confer specific benefits to the public.

Applicants argue (beginning at page 12 of Paper No. 7) the claimed invention has real-world utility as allegedly being useful for toxicology testing, drug discovery, and disease diagnosis. Applicants

argue these uses are explained in the Bedilion Declaration, the substance of which applicants assert is not rebutted by the Office action. Applicants argue there is no dispute that the claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. Applicants assert that these uses are sufficient to establish utility for the claimed polynucleotide. Applicants' arguments are not found persuasive. It is noted that the Bedilion Declaration was not present in the record at the time of drafting the Office action of Paper No. 6 and therefore, was not addressed in Paper No. 6. Regarding the substance of the Bedilion declaration, the examiner agrees with Bedilion to the extent that any polynucleotide, including the claimed polynucleotides, can be included as part of a cDNA microarray, however, this does not confer patentable utility on the claimed polynucleotides as this utility is considered a general use and not a utility that is specific and substantial. MPEP 2107.01 states, "A 'specific utility' is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention". Polynucleotides have a variety of general uses, such as for hybridization, protein expression, a component of a cDNA microarray – these uses are applicable to *any* polynucleotide and are not specific to the claimed polynucleotide. Also, the claimed polynucleotide has no substantial utility. MPEP 2107.01 states, "Utilities that require or constitute carrying our further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities". Since the specification does not disclose convincing evidence of the function of the polypeptide of SEQ ID NO:2 or a correlation between any *particular* disease or disorder and an altered level or form of the claimed polynucleotide, the results of gene expression monitoring assays using a cDNA microarray comprising the claimed polynucleotide would be meaningless without further research. MPEP 2107.01 provides an example of a substantial utility as follows: "An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a 'real world' context of use". As stated above, the specification does not disclose a correlation between any *particular* disease or disorder and an altered level or form of the claimed polynucleotide. MPEP 2107.01 also provides examples of utilities that are *not* substantial, including: "A method of assaying for or identifying a material that itself has no specific and/or substantial utility". The claimed polynucleotide

has no specific and/or substantial utility, therefore, the use of a cDNA microarray for measuring levels of the claimed polynucleotide is not substantial.

Beginning at page 13 of Paper No. 7, applicants refer to the Bedilion declaration as explaining the many reasons why a person skilled in the art reading the instant application would have understood this application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, such as a probe for expression of the polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. Specifically, applicants quote from the Bedilion declaration that a person skilled in the art would have been able to use the claimed polynucleotide in gene expression monitoring to develop new drugs for the treatment of disorders associated with increased or decreased phosphate levels. Applicants' arguments are not found persuasive. The instant specification does not substantiate a link between the claimed polynucleotides and any *specific* disorder associated with increased or decreased phosphate levels. The specification merely discloses that the claimed polynucleotide encodes a polypeptide that is structurally related to a sodium-dependent phosphate transporter and that they are expected to be involved in phosphate transport (see for example page 22 of the instant specification). MPEP 2107.01 states, "Utilities that require or constitute carrying our further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities". Since the specification does not disclose convincing evidence of the function of the polypeptide of SEQ ID NO:2 or a correlation between any *particular* disease or disorder and an altered level or form of the claimed polynucleotide, the results of gene expression monitoring assays using a cDNA microarray comprising the claimed polynucleotide would be meaningless without further research. MPEP 2107.01 provides an example of a substantial utility as follows: "An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a 'real world' context of use". As stated above, the specification does not disclose a correlation between any *particular* disease or disorder and an altered level or form of the claimed polynucleotide. The specification does not disclose any results that would enable a skilled artisan to draw any conclusions regarding a disorder, namely, that the expression of the

claimed polynucleotide is expressed at an altered level or form as compared to the corresponding normal tissue. Many genes expressed in diseased tissues have no connection to the disease itself and are not targets for drug development or toxicology.

Beginning at the last paragraph of page 13 of Paper No. 7, applicants refer to the opinion of Dr. Bedilion who states that a person skilled in the art at the time of the invention would have concluded that a cDNA microarray containing the claimed polynucleotide would be a more useful tool than a microarray lacking the claimed polynucleotide in connection with conducting gene expression monitoring studies on proposed or actual drugs for disorders associated with increased or decreased phosphate levels for purposes of evaluating their efficacy and toxicity. Applicants' arguments are not found persuasive. As previously stated, the instant specification has not established the claimed polynucleotides as being expressed at an altered level or form in a diseased tissue as compared with the corresponding normal tissue. As applicants have provided no evidence that the claimed polynucleotides are involved in disorders associated with altered phosphate levels, if, for example, the claimed polynucleotide was a component of a microarray and a test compound resulted in decreased expression of the claimed polynucleotide, further experimentation would be required to interpret the hybridization results. Disclosure of the claimed polynucleotide as being expressed at an increased level in a specific disorder associated with altered levels of phosphate as compared with the corresponding normal tissue would provide a skilled artisan with an indication that a given test compound that decreased expression of the polynucleotide is a potential candidate drug. However, this disclosure has not been provided and the claimed polynucleotides may very well be expressed at equivalent levels in normal tissues. In the absence of any disclosed relationship between the claimed polynucleotide or the encoded protein and any *specific* disease or disorder, any information obtained from an expression profile would only serve as the basis for further experimentation on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Beginning at the first full paragraph of page 14, applicants discuss the Bedilion declaration's detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations. Applicants point to Dr. Bedilion's pages of text and numerous subparts explaining the importance of this technology. Applicants point to Dr. Bedilion's explanation that those skilled in the art at the time of the invention without any doubt would have appreciated the criticality of toxicity testing. Applicants' arguments are not found persuasive. While there is no doubt that cDNA microarray technology is an extremely valuable technique in gene expression monitoring, toxicology testing, and drug efficacy testing, the claims are not drawn to this technique. Instead, the claims are directed to polynucleotides that have not been disclosed as being associated with any particular disease or condition. As stated above, any polynucleotide can be a component of a microarray. Thus, this asserted utility is not specific. Determining the relationship between the claimed polynucleotides and any *specific* disease or disorder based on the teachings of the instant specification would require significant further research. Therefore, this asserted utility is also not substantial.

Beginning at the bottom of page 14 of Paper No. 7, applicants assert the Bedilion declaration establishes that persons skilled in the art, guided by the instant specification, at the time of the invention would have wanted their cDNA microarrays to comprise the claimed polynucleotide, because a microarray comprising the claimed polynucleotide would provide more useful results in the kind of gene expression monitoring studies than microarrays lacking the claimed polynucleotide. Applicants' arguments are not found persuasive. The specification has not linked the claimed polynucleotide with any *specific* disease state or disorder. Incorporating the claimed polynucleotide into a microarray would not make the microarray any more valuable than adding any other polynucleotide. The asserted utility is not specific to the claimed polynucleotide.

Beginning at the top of page 15 of Paper No. 7, applicants argue the examiner does not address the asserted fact that, as described in the specification, the claimed polynucleotide can be used as highly specific probes to measure both the existence and amount of complementary mRNA sequences known to be expression products of the claimed polynucleotides. Applicants conclude that the claimed invention is

not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine. Applicants' arguments are not found persuasive. As stated above, *any* polynucleotide is a highly specific probe for itself or its complement, or any mRNA that can be transcribed from it. Such can be said for *any* polynucleotide. MPEP 2107.01 provides an example of a utility that is *not* substantial as follows: "A method of assaying for or identifying a material that itself has no specific and/or substantial utility". The claimed polynucleotide has no specific and/or substantial utility, therefore, the use of a cDNA microarray comprising the claimed polynucleotide for measuring levels of the claimed polynucleotide is *not* substantial.

Applicants argue that, given that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. Applicants cite case law as allegedly relevant to the patentable utility of research tools. Applicants' arguments are not found persuasive. It is true that a scale, gas chromatograph, screening assays, and nucleotide sequencing techniques have utility as research tools. However, such tools present a result that requires no further experimentation for interpretation, e.g., a scale provides the weight of an object that requires no further experimentation for interpretation of the result. A more representative analogy to the claimed polynucleotides and array would be that of a scale without an identifiable unit of measure - one could place an object on the scale, however, further experimentation would be required to interpret the result and determine the weight of the object. Similarly, as applicants have provided no information regarding altered expression of the claimed polynucleotide, additional experimentation would be required to interpret a result of altered polynucleotide expression obtained using a microarray comprising the claimed polynucleotides. MPEP 2107.01 provides an example of a substantial utility as follows: "An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a 'real world' context of use". As stated above, the specification does not disclose a correlation between any *particular* disease or disorder and an altered level or form of the claimed polynucleotide. Therefore, the

assertion that the claimed polynucleotide has patentable utility as a probe in, or a member of, a microarray is not substantial.

Beginning at the third full paragraph of Paper No. 7, applicants argue there can be no reasonable dispute that persons skilled in the art have numerous uses for information about relative gene expression including understanding the effects of a potential drug for treating disorders associated with increased or decreased phosphate levels. Applicants argue that, since the specification discloses the claimed polynucleotide to be expressed in brain tumor cells and expresses a protein that is allegedly a member of a class of proteins that regulate intracellular phosphate levels, there can be no dispute that an ordinarily skilled artisan could derive more information about relative gene expression than without it. Applicants' arguments are not found persuasive. While the specification does indicate that the nucleic acid of SEQ ID NO:2 is expressed in brain tumor tissues (see page 35 of the instant specification), there is no indication that expression of SEQ ID NO:1 is specific for brain tumor tissues. Nor is there indication that this nucleic acid has altered expression in tumor or brain tumor tissue as compared to normal tissue. The specification does *not* disclose the claimed polynucleotide as being expressed at an altered level or form in any particular disease or disorder as compared to the corresponding normal tissue(s). Other than functional assignment of the polypeptide of SEQ ID NO:1 based solely on sequence identity, there is no further indication that the polypeptide of SEQ ID NO:1 is involved in phosphate transport. Furthermore, even if it can be assumed that the claimed polynucleotides play a role in a disorder associated with increased or decreased phosphate levels, determining which disorder(s) is/are involved and how the claimed polynucleotides are altered during the disorder requires significant further research. Absent such a disclosure of altered levels or forms of a gene in diseased tissue as compared with the corresponding normal, i.e., healthy, tissue, further experimentation is necessary for to use the claimed polynucleotide to derive information about a potential drug candidate. Thus, the asserted utility is not substantial.

Beginning at the bottom of page 15 of Paper No. 7, applicants refer to Dr. Bedilion's discussion of the Brown et al. patent (US Patent 5,807,522, cited by applicants), attached to the declaration. Dr. Bedilion characterizes the patent as providing evidence that microarrays can be used in numerous genetic

applications, including monitoring of gene expression in different tissue types, disease states, in response to drugs, and in response to potential toxins. Applicants' arguments are not found persuasive. The claims of the Brown et al. patent are drawn to methods of forming microarrays (see, for example, claim 1 of the Brown et al. patent). Methods of forming a microarray have patentable utility. However, what the research tool measures does not necessarily have patentable utility, such as the object being weighed by the scale. Furthermore, contrary to a scale, which provides an identifiable unit of weight, a microarray comprising the claimed polynucleotide would generate a result that requires further research for a real world application. Thus, the asserted utility is not substantial.

Beginning at the middle of page 16 of Paper No. 7, applicants refer to the references of Rockett et al. (*Xenobiotica* 29:655, cited by applicants) and Lashkari et al. (*Proc Natl Acad Sci USA* 94:8945, cited by applicants) who discuss microarrays and gene expression technology with respect to drug screening and toxicology testing. Applicants' arguments are not found persuasive. Applicants' arguments and alleged supporting evidence merely indicate that microarray technology is important and useful to the scientific community. These publications fail to demonstrate the claimed invention has *any* patentable utility. The use of the claimed uncharacterized polynucleotides in such studies would provide no more information than the use of any other uncharacterized polynucleotide. The asserted utility for the claimed polynucleotide is not specific to the claimed polynucleotide as stated above. Furthermore, due to the lack of disclosure of a correlation between the claimed polynucleotides and a particular disorder, the asserted utility is also not substantial, as discussed above.

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is allegedly "well-established".

Beginning at page 17 of Paper No. 7, applicants argue that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease and that these uses are "well-established". Applicants cite the references of Rockett et al. (*Xenobiotica* 29:655), Nuwaysir et al. (*Mol Carcinogen* 24:153), Steiner et al. (*Tox Lett* 112-113:467), Rockett et al. (*Environ Health Perspectives*

107:681), an email from Dr. Cynthia Afshari to an Incyte employee, and examples as set forth at page 19 of Paper No. 7 that allegedly support applicants' assertions. Applicants argue that, because the examiner has allegedly failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and disease diagnosis, the rejections should be withdrawn. Each of these uses will be addressed individually, because the facts and issues directed to each use are distinct and separable. First, applicants argue that toxicology testing is a well-established utility and concludes that the claimed polynucleotides could be used in this manner and that the claimed invention possesses utility. However, for a utility to be "well-established" it must be specific, substantial and credible. In this case, as indicated at page 10, lines 12-13 of Paper No. 7, "all polynucleotides expressed in humans have utility in toxicology testing". However, the specification fails to disclose the methods and information necessary for a skilled artisan to use the claimed polynucleotide for toxicology testing. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or polynucleotides. Thus, such a utility is *not* specific and does *not* constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form and would thus require further research for its implementation. Moreover, use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gleaned from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility that would apply to virtually every member of a general class of materials, such as any collection of proteins or polynucleotides. Even if the expression of applicants' claimed polynucleotide is affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotides have no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information generated using this nucleic acid may have.

With regard to drug discovery and development, applicants mention expression profiling as one use of the claimed polynucleotide. Applicants refer to recent developments as providing evidence that the benefits of this information are already beginning to manifest themselves. However, applicants are incorrect in asserting that the efficacy (ability to produce a desired effect) of a compound could be evaluated from the result of a transcript image because there is no way to assess the meaning of any individual hit obtained from this procedure. The first requirement is that one must know the biological significance of the polynucleotide(s) which is/are being evaluated. Without this information, the results of the transcript image are useless because one would not inherently recognize how to interpret the result of increased or decreased polynucleotide expression or even what significance could be attributed to such changes in expression profiles. As such information has not been provided in the specification, further experimentation is required to identify a "real world" use for the claimed polynucleotide.

With regard to diagnosis of disease, in order for a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in tissue that is derived from brain tumor cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed polynucleotide and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many polynucleotides are expressed at equal levels and in identical forms in both normal *and* diseased tissues. Therefore, one necessarily needs to know, e.g., that the claimed polynucleotide is either present only in brain tumor tissue to the exclusion of normal tissue or is expressed in higher levels in brain tumor tissue compared to normal tissue. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotides as a diagnostic for disease(s). However, in the absence of any disclosed relationship between the claimed polynucleotides or encoded proteins and any disease or disorder and the lack of any correlation between the claimed polynucleotides or the encoded proteins with any known

disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

C. The similarity of the polypeptide encoded by the claimed invention to another polypeptide of undisputed utility is asserted to demonstrate utility

Beginning at the bottom of page 19 of Paper No. 7 applicants argue that the utility of the claimed polynucleotide can be imputed based on the relationship between NAPTR (SEQ ID NO:1 encoded by SEQ ID NO:2) and another polypeptide of unquestioned utility, human renal sodium phosphate transport protein (NPT1). Applicants argue that the polypeptide encoded by SEQ ID NO: 2 shares more than 48 % sequence identity over 401 amino acid residues with NPT1. Applicants argue that NAPTR (SEQ ID NO:1), NPT1, and rat brain-specific sodium-dependent inorganic phosphate cotransporter all share a *potential* N-glycosylation site and have rather similar hydrophobicity plots. Applicants conclude that these results are sufficient to demonstrate a reasonable probability that the utility of NPT1 can be imputed to the claimed polynucleotide. Applicants cite Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) as evidence that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Applicants argue the Office must accept applicants' demonstration that the homology between NAPTR (SEQ ID NO:1) and NPT1 demonstrates utility by a reasonable probability unless evidence or sound scientific reasoning is presented such that a person of ordinary skill in the art would doubt utility. Applicants argue that none of the references cited by the examiner (van de Loo et al. *Proc Natl Acad Sci USA* 92:6743-6747, Seffernick et al. *J Bacteriol* 183:2405-2410, and Bork *Genome Res* 10:398-400) suggests that functional homology cannot be inferred by a reasonable probability in this case. Applicants argue that none of the cited references contradicts the basic "rule" of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) that two unrelated polypeptides sharing more than 40%

sequence homology over 70 amino acid residues is exceedingly small. Applicants argue the cited references at best demonstrate that it is difficult to make predictions about function with certainty and not reasonable probability. Applicants' arguments are not found persuasive.

As far as the asserted "unquestioned" utility of NPT1, the instant application is not drawn to nucleic acids encoding NPT1, and, to that extent, the utility of NPT1 is not at issue. As the specification has *not* established with a reasonable probability that the polypeptide of SEQ ID NO:1 shares the same function as NPT1 or belongs to the class of phosphate cotransporters, the utility of NPT1 or phosphate transport proteins as a class is not at issue. While the polypeptide encoded by SEQ ID NO:2 may share more than 48 % sequence identity over 401 amino acid residues with NPT1, this is no indication that the polypeptide encoded by SEQ ID NO:2 shares the same function as NPT1. It is well known in the art that structural identity is not predictive of functional similarity. One of ordinary skill in the art would recognize that, while sequence identity between two polypeptides can be used to *predict* function, empirical analysis is the only true method of determining a protein's function with a reasonable probability. As a specific example, Scott et al. (*Nat Genet* 21:440-443) teach a polypeptide that has 45 % sequence identity (it is noted that SEQ ID NO:1 similarly shares 48 % identity with NPT1) with a human sulfate transporter and that, based on structural homology has been proposed to function as a sulfate transporter (page 440, left column, abstract). However, an empirical analysis of the protein measuring its ability to transport various ions revealed the protein is actually a chloride-iodide transport protein (page 441, left column, third full paragraph). Scott et al. "conclude that pendrin does not function as a sulfate transporter, as suggested by its close homology to other sulfate transporters, but instead functions as a sodium-independent transporter of chloride and iodide. **These results underscore the importance of confirming the function of newly identified gene products even when database searches reveal significant homology to proteins of known function**" (emphasis added; page 441, left column, third full paragraph). Thus, a skilled artisan would recognize that the function of a polypeptide cannot be assigned based on solely on sequence identity, and would conclude that the specification has

not established with a reasonable probability that the polypeptide of SEQ ID NO:1 shares the same function as NPT1 or belongs to the class of phosphate cotransporters.

Also, while NAPTR (SEQ ID NO:1), NPT1, and rat brain-specific sodium-dependent inorganic phosphate cotransporter may all share a *potential* N-glycosylation site, an ordinarily skilled artisan would recognize that nearly all full-length proteins exhibit a *potential* N-glycosylation site and therefore, would not be a factor in a determination of whether NAPTR (SEQ ID NO:1) and NPT1 share the same function.

Furthermore, while NAPTR (SEQ ID NO:1), NPT1, and rat brain-specific sodium-dependent inorganic phosphate cotransporter may have rather similar hydrophobicity plots, such plots have been shown to be similar even among proteins with relatively low sequence homology that exhibit different functions. For example, Vrljic et al. (*J Mol Microbiol Biotechnol* 1:327-336) analyze the hydrophobicities of three proteins that function in the transport of different molecules (page 329, Figure 2) revealing strikingly similar hydrophobicity plots. Thus, based on the cited references, an ordinarily skilled artisan would recognize that a protein's function *cannot* be assigned based on structural identity alone. Empirical evidence is required to verify the function of a polypeptide, which has not been provided in the instant case. Thus, one of ordinary skill in the art would not recognize a reasonable probability that the polypeptide of SEQ ID NO:1 encoded by SEQ ID NO:2 has utility similar to NPT1.

Even if the specification provided sufficient evidence to convince an ordinarily skilled artisan of a reasonable probability that the polypeptide of SEQ ID NO:1 shares the same function as NPT1, which it does not, one of skill in the art would recognize that polypeptides with similar function do not necessarily have similar utilities. Tenenhouse et al. (*Am J Physiol* 275:F527-F534) teach that NPT1 and NPT2, while being phosphate transporters and belonging to the family of phosphate transport proteins, exhibit differential expression (see page F529). Thus, for example, if NPT2 expression was shown to be altered to a disorder of the intestine, this would not automatically suggest that NPT1 expression levels in the liver would also be altered. In fact, further experimentation would be required to confirm or negate this prediction.

It is noted that applicants improperly attempt to apply an alleged "rule" of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) to the asserted 48 % identity between NAPTR (SEQ ID NO:1) and NPT1. Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) clearly state that these comparisons "have been assessed **using proteins whose relationships are known reliably from their structures and functions**, as described in the SCOP database" (page 6073, abstract). The art recognizes the proteins within the SCOP database have been *fully characterized* – functionally by empirical laboratory experiments and structurally by generating a three-dimensional structure of the proteins (see for example Murzin et al. *J Mol Biol* 247:536-540). In the instant case, the function of NAPTR (SEQ ID NO:1) has not been empirically determined nor has the three-dimensional structure been solved for comparison with NPT1. The function of NAPTR has been assigned solely on the basis of a relatively low sequence identity to NPT1. Thus, an ordinarily skilled artisan would recognize that applicants' alleged "rule" of Brenner et al. does not apply to a functional assignment of NAPTR based solely on 48 % sequence homology to NPT1. Instead, Brenner has expressed his views on functional annotation of a protein based solely on sequence analysis in a manuscript titled "Errors in Genome Annotation" (*Trends Genetics* 15:132-133). In this reference, Brenner (*Trends Genetics* 15:132-133) teaches that laboratory experiments are required to verify a protein's function (page 132, left column, second paragraph) and describes the errors that are inherent in predicting function based on sequence identity. For example, Brenner (*Trends Genetics* 15:132-133) states, "[w]ithout laboratory experiments to verify the computational methods and their expert analysis, it is impossible to know for certain [whether the function assigned to a protein by annotation is correct]" (page 132, left column, second paragraph). Thus, applicants' argument that none of the previously cited references (van de Loo et al. *Proc Natl Acad Sci USA* 92:6743-6747, Seffernick et al. *J Bacteriol* 183:2405-2410, and Bork *Genome Res* 10:398-400) contradicts the basic "rule" of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) is without merit as the teachings of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) do not apply. Thus, a skilled artisan would recognize that the function of a polypeptide cannot be assigned based on solely on sequence identity, and would conclude that the specification has *not* established with a reasonable probability that the polypeptide of SEQ ID NO:1

shares the same function as NPT1 or belongs to the class of phosphate cotransporters, particularly in view of the teachings of Scott et al.

D. Objective evidence is alleged to corroborate the utilities of the claimed invention

Beginning at page 21 of Paper No. 7, applicants argue that a "real-world" utility exists if actual use or commercial success can be shown. Citing case law, applicants state that such a showing is conclusive proof of utility. Applicants argue that a vibrant market has developed for databases containing all expressed genes, including those of Incyte, the real party at interest. Applicants state Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven valuable, and that the databases including the claimed polynucleotide would be even more valuable. Applicants' arguments are not found persuasive. The case law indicates that a rejection under 35 U.S.C. § 101 *for lack of operability* can be overcome by a showing of actual use or commercial success. The instant issue is whether or not the asserted utilities meet the three-pronged test for credibility, specificity, and substantiality. Such is not necessarily addressed by a showing of commercial success or actual use. As argued previously, many products that lack patentable utility enjoy commercial success, are used, and are considered valuable and applicants' asserted utilities are neither substantial, specific, nor credible. Furthermore, while applicants present evidence showing that the database is commercially valuable, there is no evidence to suggest that the database is any more or less valuable with the inclusion of the claimed polynucleotide.

III. The patent examiner's rejections are allegedly without merit.

Beginning at the bottom of page 21 of Paper No. 7, applicants argue that, rather than responding to the evidence allegedly demonstrating utility, the examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the clamed polynucleotides are not "specific and substantial asserted" utilities. Applicants argue the Office action is incorrect both as a matter of law and as a matter of fact. Applicants' arguments are not found persuasive. The claimed invention has no well-

established use and there is no specific, substantial and credible use for the claimed invention, even after full consideration of the "evidence" as provided in the specification. Applicants' arguments will be addressed in more detail as described below.

A. The precise biological role or function of an expressed polynucleotide is alleged as being not required to demonstrate utility

Applicants characterize the examiner's rejection as being based on the grounds that, without information as to the precise biological role of the claimed invention, the claimed invention lacks specific patentable utility. Applicants argue that, according to the Office action, it is not enough that a person skilled in the art could use and would want to use the claimed invention either by itself or in a microarray, but that applicants are also required to provide a specific and substantial interpretation of the results generated in a given expression analysis. Applicants argue that specific and substantial interpretations regarding biological function may be required by technical journals, but are not necessary for patents. Applicants state the relevant question is not how or why the invention works, but whether the invention provides an identifiable benefit. Applicants argue that the present invention meets this test. Applicants argue that the threshold for patentable utility is low and that only throwaway utilities are insufficient, and that knowledge of biological function is not required. Applicants' arguments are not found persuasive. Applicants arguments have mischaracterized the examiner's position. The examiner has fully considered applicants' "evidence" demonstrating utility and, in accordance with 35 USC 101 has determined the claimed invention to lack patentable utility. Furthermore, the rejection never states that the precise biological role of a polynucleotide is required for it to possess patentable utility (see item 4 of Paper No. 6). If a polynucleotide is disclosed as being differentially expressed in a disease or disorder, even if nothing is known or hypothesized about the activities of the encoded polypeptide, then the polynucleotide has patentable utility as a disease marker and in the toxicology/drug screening microarray assays discussed at length by applicants (see the example of Shattuck-Eidens et al. in US Patent 5,693,473 provided above). However, if a specification does not disclose such information, as is the

instant case, then there is no patentable utility. For example, if the claimed polynucleotide were used in a microarray for toxicology testing and if a compound caused the claimed polynucleotide to be expressed at a decreased level in a microarray, what information does this provide, other than to initiate further experimentation. In view of the specification, a skilled artisan would recognize that the determination of whether a compound is potentially therapeutic or deleterious requires significant further research, and thus the asserted utility is not substantial. Also, any expressed polynucleotide *can* be used in a microarray – just as any polynucleotide can be used for protein expression and thus the asserted utility is also not specific.

B. Membership in a class of useful products can be proof of utility

Beginning at page 23 of Paper No. 7, applicants assert the examiner has refused to impute the utility of the members of the phosphate transporter family to NAPTR (SEQ ID NO:1). Applicants argue the examiner takes the position that utility of the claimed polynucleotides cannot be imputed unless applicants identify which particular biological function within the class of phosphate transporters is possessed by NAPTR. Applicants argue the Office would require that all phosphate transporters possess a "common" utility in order to demonstrate utility by membership in a class of phosphate transporters. Applicants state the case law requires only that the class not contain a substantial number of useless members. Applicants argue the examiner has treated NAPTR as if it was in a general class of all polynucleotides, rather than the phosphate transporter class. Applicants conclude that the examiner has not presented any evidence that the phosphate transporter class of proteins has any, let alone a substantial number, of useless members. Applicants' arguments are not found persuasive. As described above, applicants *predict* their protein shares function with NPT1 and belongs to the class of phosphate transport proteins based on a relatively low sequence identity, a *predicted* N-glycosylation site, and a hydrophobicity plot. As stated above, based on such evidence a skilled artisan would recognize that the function of a polypeptide cannot be assigned based on solely on sequence identity, and would conclude that the specification has *not* established with a reasonable probability that the polypeptide of SEQ ID

NO:1 shares the same function as NPT1 or belongs to the class of phosphate cotransporters, particularly in view of the teachings of Scott et al. See II. part C. above. The class of proteins considered to be phosphate transporters is diverse as taught by Tenenhouse et al., "physiological and molecular studies have provided evidence for heterogeneity of Na+_Pi cotransporter systems" (page F531, right column). Thus, the class of phosphate transport proteins cannot be used to predict utility for a new polypeptide that is included in the class based solely on sequence identity to another member of the class. Furthermore, the specification has provided no asserted *specific, substantial, and credible* utility for the *entire* class of phosphate transporters and, there is no apparent well-established utility for this *entire* class of proteins.

Beginning at the middle of page 24 of Paper No. 7, applicants argue that even if the examiner's common utility criterion were correct, the phosphate transport family would meet it. Applicants argue the phosphate transporter family is known to regulate intracellular phosphate levels, and the person of ordinary skill in the art need not know anything more about the claimed invention in order to be able to use it and the Office action presents no evidence to the contrary. Applicants argue the Office action concludes that a skilled artisan would need to know whether any given phosphate transporter carries out a particular role in intracellular phosphate level regulation and that NAPTR is useful only for further study of NAPTR. Applicants argue that knowledge that NAPTR is a phosphate transporter is sufficient to make it useful for diagnosis and treatment of disorders associated with altered phosphate levels. Applicants argue NAPTR has been shown to be expressed in human brain tumor tissues. Applicants conclude that these facts must be accepted as true in the absence of evidence or sound scientific reasoning to the contrary. Applicants' arguments are not found persuasive. As stated above, the specification fails to provide convincing evidence that NAPTR is a phosphate transporter (see particularly II part C above) and there is no apparent utility for the *entire* class of phosphate transport proteins, particularly in view of the teaching of Tenenhouse et al. who teaches that there is heterogeneity among phosphate transporters. As previously stated, the specification provides no information regarding altered level or form of the claimed polynucleotide for use in diagnoses or treatment of disorders associated with altered phosphate levels.

Thus, further experimentation would be required to determine if SEQ ID NO:1 indeed functions as a phosphate transporter and, if so, what if any connection can be made to a specific disorder. While NAPTR may be expressed in brain tumor tissues, the specification has provided no evidence that NAPTR is *not* expressed in other tissues or at a level or form that is different in brain tumor tissues from that of normal tissues. As such, significant further research would be is necessary for the skilled artisan to use the claimed nucleic acids in a real world context, and thus the asserted utility is not substantial.

C. The uses of the claimed polynucleotides in toxicology testing, drug discovery, and disease diagnosis are allegedly practical uses beyond mere study of the invention itself

Beginning at page 25 of Paper No. 7, applicants argue the rejection is incorrectly based on the grounds that the use of an invention as a tool for research is not a substantial use. Applicants state that only a limited subset of research uses are not substantial: those in which the only known use for the claimed invention is to be an object of further study, thus merely inviting further research. Applicants cite case law allegedly supporting their argument that a material cannot be patentable if it has some other, additional beneficial use in research. Applicants' arguments are not found persuasive. As discussed above, whereas a scale or gas chromatograph has patentable utility as a research tool as providing a result that can be readily used, in this case, the use of the polynucleotide would require further experimentation as described above. The claimed polynucleotide is not disclosed as having a property (such as a differential pattern of expression in diseased tissue) that can be identifiably and specifically useful without further, additional experimentation. The claimed invention is, in fact, the object of further study, merely inviting further research. None of the utilities asserted for the claimed polynucleotide meets the three-pronged test of being specific, substantial and credible.

Beginning at the top of page 26 of Paper No. 7, applicants argue the claimed invention has a beneficial use in research for use in toxicology testing, drug discovery, and disease diagnosis. Applicants argue the claimed polynucleotide is a tool not an object of research. Applicants argue the result of gene

expression monitoring using the claimed invention is not merely to study the polynucleotide itself, but to study properties of tissues, cells, and potential drug candidates and toxins. Applicants argue that without the claimed invention, information regarding properties of tissues, cells, and potential drug candidates and toxins is less complete. Applicants argue the use of the invention is substantial and specific. Applicants argue that although all polynucleotides expressed in humans have utility for toxicology testing, this does not preclude the utility from being specific and substantial. Applicants argue a toxicology test using a particular polynucleotide is dependent on the identity of that polynucleotide. Applicants argue the result obtained from toxicology testing is specific to both the compound and polynucleotide being tested. Applicants argue no two human-expressed polynucleotides are interchangeable for toxicology testing due to the identity of the polynucleotide. Applicants argue it is not necessary to know the biological function and disease association of the polynucleotide in order to perform such toxicology tests. Applicants argue at the very least the polynucleotides are useful as controls for toxicology testing. Applicants' arguments are not found persuasive. As stated above, the examiner agrees with applicants' argument to the extent that the utility requirement of 35 USC 101 does not require knowledge of biological function to prove utility. It is evident from the example of Shattuck-Eidens et al. that utility for a polynucleotide does not require knowledge of biological function. Applicants' line of argument that all polynucleotides expressed in humans have utility in toxicology testing would appear to support the examiner's argument that the claimed polynucleotide has no *specific* utility. If any polynucleotide expressed in a human has utility in toxicology testing, then that polynucleotide has no *specific* utility as all polynucleotides would have such use. Therefore, any human polynucleotide could be used as a control in toxicology testing and thus this use would not be a *specific* utility. If a specific disease state were correlated with the presence of altered levels or form of a given polynucleotide, then that polynucleotide would have *specific* utility as an indicator of disease. In order to clarify this point, the following example is provided: all polynucleotides have use for protein expression and the amino acid sequence of the expressed protein would be specific and dependent upon the identity of the polynucleotide, i.e., the nucleotide sequence of the encoding nucleic acid. However, as all nucleic acids have utility for protein expression, this utility is not specific.

Beginning at page 26 of Paper No. 7, applicants use the example of a histone gene expressed in humans as having a specific and substantial use in toxicology testing. Applicants argue a histone gene may not be a suitable therapeutic target, but the gene is allegedly excellent subject for toxicology testing of drugs targeted to other genes. Applicants argue a drug that alters expression of a histone gene is toxic because disruption of said histone gene would have undesirable side effects. Applicants conclude that a histone gene is a good measure of toxicity when analyzing compounds targeted to another gene because that histone gene cannot be replaced with a different gene. Applicants' arguments are not found persuasive. Applicants erroneously attempt to analogously compare a histone gene with the claimed polynucleotide. As one of skill in the art would recognize, histone is ubiquitously expressed and is necessary for cell survival and function. This contrasts with the instant case where, as previously stated, the function of SEQ ID NO:1 is uncharacterized and the physiological implications of altered expression of SEQ ID NO:1-encoding polynucleotides is unknown. The information provided by applicants regarding the histone gene, i.e., disruption may kill a patient, is lacking for the claimed polynucleotide. As previously stated, there is no indication of the effects of altered expression of the claimed nucleic acid in the specification and there is no indication as to how altered expression of the claimed polynucleotide would be useful, i.e., as a marker of toxicity of a compound. Thus, further experimentation is required for a real world use of the claimed invention and thus, the claimed invention has no substantial utility.

D. The Office action allegedly fails to demonstrate that a person skilled in the art would reasonably doubt the utility of the claimed invention.

Beginning at page 27 of Paper No. 7, applicants argue the claims have been rejected based principally on citations to scientific literature identifying some of the difficulties in predicting protein function. Applicants state that it is incorrect to question whether utility can be imputed to the claimed invention based on its homology to another polypeptide. Applicants characterize the cited literature as not being inconsistent with applicants' alleged "proof" of homology by a reasonable probability. Applicants argue that the examiner has not made a showing that the assertion of utility cannot be

accepted as true based on evidence that a person of ordinary skill would doubt the asserted utility by a reasonable probability. Applicants' arguments are not found persuasive. Specifically, the reference of Scott et al. (*Nat Genet* 21:440-443) has been provided to demonstrate that sequence identity between two transport proteins is *not* predictive of functional similarity. As previously stated, Scott et al. teach a polypeptide that has 45 % sequence identity (it is noted that SEQ ID NO:1 similarly shares 48 % identity with NPT1) with a human sulfate transporter and that, based on structural homology has been proposed to function as a sulfate transporter (page 440, left column, abstract). However, an empirical analysis of the protein measuring its ability to transport various ions revealed the protein is actually a chloride-iodide transport protein (page 441, left column, third full paragraph). Scott et al. "conclude that pendrin does not function as a sulfate transporter, as suggested by its close homology to other sulfate transporters, but instead functions as a sodium-independent transporter of chloride and iodide. **These results underscore the importance of confirming the function of newly identified gene products even when database searches reveal significant homology to proteins of known function**" (emphasis added; page 441, left column, third full paragraph). Thus, based on this evidence, the person of ordinary skill in the art would *reasonably* doubt whether the polypeptides encoded by the claimed polynucleotides have a functions similar to NPT1, a phosphate transport protein.

Beginning at page 27 of Paper No. 7, applicants argue that, despite the cited references, identification of the particular function of what is claimed is not needed to fulfill the utility requirement of the law. This is not found to be persuasive, because the specification has not asserted any utility for the claimed polynucleotides that is credible, specific and substantial, regardless of whether or not the asserted utility is based on the encoded polypeptide's function. As stated above, if the specification *had* provided a specific, substantial and credible assertion of utility for the claimed polynucleotides unrelated to the function of the encoded polypeptides, such would have been accepted, and a rejection under 35 U.S.C. § 101 would not have been made.

Applicants argue the cited references of van de Loo et al., Seffernick et al., and Bork, fail to support the outstanding rejection. Applicants cite Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078)

as evidence that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Applicants argue the Office must accept applicants' demonstration that the homology between NAPTR (SEQ ID NO:1) and NPT1 demonstrates utility by the "reasonable correlation" standard as set by case law. Applicants' arguments are not found persuasive. As stated above, applicants improperly attempt to extrapolate the results of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) to the asserted 48 % identity between NAPTR (SEQ ID NO:1) and NPT1. Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) clearly state that these comparisons "have been assessed **using proteins whose relationships are known reliably from their structures and functions**, as described in the SCOP database" (page 6073, abstract). The art recognizes the proteins within the SCOP database have been *fully characterized* – functionally by empirical laboratory experiments and structurally by generating a three-dimensional structure of the proteins (see for example Murzin et al. *J Mol Biol* 247:536-540). In the instant case, the function of NAPTR (SEQ ID NO:1) has not been empirically determined nor has the three-dimensional structure been solved for comparison with NPT1. Thus, there is no "reasonable correlation" between the results of Brenner et al. and the functional assignment of NAPTR based solely on 48 % sequence homology to NPT1. Instead, Brenner (*Trends Genetics* 15:132-133) teaches that laboratory experiments are required to verify a protein's function (page 132, left column, second paragraph), which clearly is not the case.

Applicants argue that, contrary to the examiner's assertions, the use of sequence comparison to predict protein function is supported by Bork (2000, Genome Research 10:398-400) who allegedly discloses a 70% accuracy rate in bioinformatics-based predictions and a 90% accuracy rate when predicting functional "features". Applicants argue that based on this teaching, a skilled artisan would more likely than not believe the asserted utility. Applicants' arguments are not found persuasive. It appears applicants have ignored the teachings by Bork, particularly the footnote to Table 1 of Bork, which states that the evidence provided is a crude estimate and that "numbers in Table 1 are often overestimates because the test sets used are usually not representative of all sequences". Thus there is no "reasonable correlation" between the results of Bork and the functional assignment of NAPTR based

solely on 48 % sequence homology to NPT1. The reference of Bork, particularly in view of the reference of Scott et al. would fail to more likely than not convince a skilled artisan of applicants' asserted utility.

Beginning at the bottom of page 28 of Paper No. 7, applicants criticize the references of van de Loo, Broun et al., and Seffernick et al. Applicants argue these references, while demonstrating the difficulty in obtaining a precise functional assignment, do not contradict the findings of Bork that, in the majority of cases, protein function is accurately predicted by sequence homology. Applicants argue the cited references do not provide any evidence that a skilled artisan would more likely than not doubt that NAPTR possesses the utility of NPT1 phosphate transporter. Applicants' arguments are not found persuasive. It is noted that the instant claims are drawn to nucleic acids encoding NAPTR, not NPT1, therefore, the utility of NPT1 has not been questioned as nucleic acids encoding NPT1 are not the subject of the instant application. The nucleic acid of SEQ ID NO:2 is distinct in structure from that of the nucleic acid encoding NPT1. If an NAPTR-encoding nucleic acid had been claimed and elected for examination in the instant application, the examiner would fully analyze claims drawn to an NPT1-encoding nucleic acid under 35 USC 101. As such claims drawn to nucleic acids encoding NPT1 are not present, the utility of NPT1 has not been questioned. Instead, it is the utility of the claimed polynucleotides that is at issue. Also, as previously stated, applicants have mischaracterized the teachings of Bork as relative to *all* functional assignments, which they clearly are not, and have ignored the specific teachings of Bork who teaches that the evidence provided is a crude estimate and that "numbers in Table 1 are often overestimates because the test sets used are usually not representative of all sequences". Based on the cited references of van de Loo, Broun et al., and Seffernick et al. and particularly the teachings of Scott et al., a skilled artisan would certainly doubt applicants' asserted utility.

Applicants argue Seffernick et al. recognize that functional assignment based on >50% are considered to reasonably sound and proteins with >98% sequence identity catalyzing different reactions is highly exceptional. Applicants argue this supports the "fact" that while a number of examples of incorrect assignment of function, this does not contradict the findings of Bork et al. who, applicants allege, teach that in general, sequence homology is an accurate method for assigning biological function.

Applicants argue the teachings of Bork do not show that errors cannot occur, but that there may be difficulties in predicting function based on sequence. Applicants argue a skilled artisan would more likely than not believe NAPTR has the utility of the family of phosphate transporter proteins. Applicants' arguments are not found persuasive. It is noted that applicants' statement by Seffernick et al. regarding >50% sequence identity has been mischaracterized. In fact, Seffernick et al. teach their result of identifying two proteins with >98% identity and having distinct functions "underlies current genome annotation efforts where functional assignments based on >50 % sequence identity are considered to reasonably sound" (page 2409, left column, middle) – thus, supporting the examiner's argument that sequence identity is not predictive of function. While it is acknowledged that Seffernick describe their findings as "highly exceptional", this reference nonetheless provides evidence that functional assignment cannot be based on sequence identity alone and should be substantiated by empirical evidence. This is further evidenced by Scott et al. who teach a polypeptide that has 45 % sequence identity (it is noted that SEQ ID NO:1 similarly shares 48 % identity with NPT1) with a human sulfate transporter and that, based on structural homology has been proposed to function as a sulfate transporter (page 440, left column, abstract). However, an empirical analysis of the protein measuring its ability to transport various ions revealed the protein is actually a chloride-iodide transport protein (page 441, left column, third full paragraph). Scott et al. "conclude that pendrin does not function as a sulfate transporter, as suggested by its close homology to other sulfate transporters, but instead functions as a sodium-independent transporter of chloride and iodide. **These results underscore the importance of confirming the function of newly identified gene products even when database searches reveal significant homology to proteins of known function**" (emphasis added; page 441, left column, third full paragraph). Thus, based on this evidence, the person of ordinary skill in the art would *reasonably* doubt whether the polypeptides encoded by the claimed polynucleotides have a functions similar to NPT1, a phosphate transport protein. Regarding the reference of Bork, applicants have again ignored the footnote to Table 1 of the Bork reference which states the evidence provided is a crude estimate and that "numbers in Table 1 are often overestimates because the test sets used are usually not representative of

all sequences". Provided the supporting evidence, it is submitted that one skilled in the art would have had substantial reason to doubt the assertion that the claimed polynucleotides encode a polypeptide having function similar to NPT1 or the family of phosphate transport proteins.

IV. By requiring the patent applicant to assert a particular or unique utility, the patent examination utility guidelines and training materials applied by the patent examiner allegedly misstate the law.

Beginning at page 30 of Paper No. 7, applicants challenge the legality of the Patent Examination Utility Guidelines. Applicants are reminded that the examiner must examine a patent application according to the guidelines set forth by the USPTO as well as the MPEP, since the examiner has no authority to disregard such guidelines or to apply his own interpretation of patent law in the examination of the application. Furthermore, as set forth in the guidelines and the MPEP, the guidelines were promulgated by the Patent Office in accordance with all applicable case law and thus are believed to be consistent therewith. Applicants are further reminded that the examiner has no authority to comment in regard to the legality of the new utility guidelines or the MPEP as set forth by the USPTO. Accordingly, it is the examiner's position that the instant claims, based on an analysis of the utility requirement of 35 USC 101 and following the current Utility Guidelines, have no specific, substantial, or credible utility.

Claim Rejections - 35 USC § 112, Second Paragraph

[9] The rejection of claim 48 as being indefinite in the recitation of "specifically hybridizable" is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 9 of Paper No. 6).

Applicants argue (beginning at page 33 of Paper No. 7) by citing case law that is allegedly relevant to the instant rejection. Applicants argue the terms hybridization, specific hybridization, and specifically hybridizable probes are defined or find support in the specification. Applicants argue the degree of complementarity necessary for a polynucleotide to be "specifically hybridizable" to a target

polynucleotide could be ascertained by a skilled artisan by considering the phrase in the context of claim 48. Applicants argue a skilled artisan would understand that the hybridization of the probe and target polynucleotides would require a certain degree of specificity in order for the claimed array to function effectively. Applicants argue a skilled artisan would reasonably conclude that this degree of specificity is that which is necessary to achieve the requisite specificity of hybridization and a skilled artisan would understand the metes and bounds of the phrase "specifically hybridizable" in the context of the claimed array. Applicants' arguments are not found persuasive.

It is noted that applicants' arguments are circular in that they define the term "specifically hybridizable" as "a nucleic acid molecule which is 'specifically hybridizable' to a target polynucleotide hybridizes 'specifically' or 'selectively' to that target polynucleotide" (see page 34, lines 7 and 8 of Paper No. 7). One of skill in the art, based on the claims and the specification, would not be able to determine the metes and bounds of the term, even in the context of claim 48. The closest definition applicants have provided to "specifically hybridizable" is the circular definition as provided above, which provides no indication of the intended scope of polynucleotides as the conditions under which specific hybridization are to take place are completely undefined. Neither the specification nor the claims provides a definition for the term "specifically hybridizable" and it is unclear as to how complementary a polynucleotide must be to be "specifically hybridizable with at least 30 contiguous nucleotides of a target polynucleotide". It is suggested that the term "specifically hybridizable" be replaced with, for example, "completely complementary".

Claim Rejections - 35 USC § 112, First Paragraph

[10] The written description rejection of claims 3, 6, 7, 9, 12, 13, 46, 48, 57, and 58 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action (see item 10 of Paper No. 6). Applicants' arguments are summarized and rebutted as follows. For applicants' convenience, the examiner's rebuttal of applicants' arguments will maintain the format as used by applicants in Paper No. 7.

A. The specification d es n t provide an adequate written descripti n of the claimed "variants" and "fragments" of SEQ ID NO:1 and SEQ ID NO:2.

Beginning at page 34 of Paper No. 7, applicants argue the claimed subject matter is either disclosed or is conventional or well known to a skilled artisan. Applicants provide alleged support for the "variants" and "fragments" as encompassed by the claims. Applicants argue that a skilled artisan would recognize polynucleotide sequences that are variants having a sequence at least 90% or 95% identical to SEQ ID NO:2, or which encode polypeptide variants having an amino acid sequence at least 90% identical to SEQ ID NO:1. Applicants argue that given a naturally-occurring polynucleotide sequence, it would be routine for a skilled artisan to recognize whether it is a variant of SEQ ID NO:2 or encoded a variant of SEQ ID NO:1. Based on this alleged "routine recognition", applicants conclude that the specification provides an adequate description of the claimed variants of SEQ ID NO:2 or polynucleotides encoding variants of SEQ ID NO:1. Similarly, applicants argue that a skilled artisan would recognize polynucleotides that are fragments of SEQ ID NO:2 or encode polypeptides that are fragments of SEQ ID NO:1. Applicants argue the sequences of SEQ ID NO:1, 2, and 5 provides the necessary framework for the recited fragments and that to recite all possible fragments would needlessly clutter the application. Applicants argue it would be routine for a skilled artisan to determine those fragments of SEQ ID NO:1 having phosphate transport activity using the disclosed assay. Based on this disclosure, applicants conclude that the specification provides an adequate description of the claimed fragments of SEQ ID NO:2 or polynucleotides encoding fragments of SEQ ID NO:1. Applicants' arguments are not found persuasive. The specification provides *only a single representative species* of the claimed genus of nucleic acids, i.e., the nucleic acid of SEQ ID NO:2 encoding a polypeptide asserted as having phosphate transport activity. The single disclosed representative species of SEQ ID NO:2 fails to provide an adequate description of the entire genus of claimed variants of SEQ ID NO:2, nucleic acids encoding variants of SEQ ID NO:1, or nucleic acids comprising fragments of SEQ ID NO:2. Applicants' alleged description of variants of SEQ ID NO:2 and nucleic acids encoding variants of SEQ ID NO:1 and nucleic acids comprising fragments of SEQ ID NO:1 (see page 36, lines 8-18) merely provides a textual

description of said variants and nucleic acids comprising fragments and provides no further structures of representative species. As such, a skilled artisan would *not* be able to visualize the structures of each member of the claimed genus. Because there is no functional limitation provided for the variants of SEQ ID NO:2 and nucleic acids encoding variants of SEQ ID NO:1, one of skill in the art would recognize that the claimed genus of variants encompass species having substantial variation of function within the genus. Similarly, one of skill in the art would recognize that the claimed genus of nucleic acids *comprising* only 20 or 60 nucleotides of SEQ ID NO:2 encompass species having substantial variation of structure and function within the genus. One of skill in the art would recognize that such variants encompass nucleotide sequences encoding polypeptides having phosphate transport activity in addition to non-functional polypeptides and polypeptides having a function other than phosphate transport activity. When there is substantial variation within a genus, one must describe a sufficient variety of species to reflect the variation within the genus. The single representative species of SEQ ID NO:2 fails to describe the entire genus of claimed nucleic acid variants and nucleic acids *comprising* fragments of SEQ ID NO:2.

1. The present claims do not define the claimed genus through the recitation of chemical structure.

Beginning at page 37 and continuing through page 38 of Paper No. 7, applicants' summarize case law citing *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed Cir 1993) and *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed Cir 1997) as court cases in which the recitation of functional characteristics of a DNA, without description of structural features has been a basis by which the courts have found invalid claims to DNA. Applicants argue the claims at issue are in contrast to the claims of the *Lilly* and *Fiers* cases as applicants allege the claimed genus of nucleic acids is defined by structure rather than function. Applicants argue there is no reliance solely on functional characteristics of the claimed nucleic acids. Applicants argue the Office has failed to base the written description inquiry "on whatever is now claimed" and fails to provide an appropriate analysis of the instant claims and how they differ from those of the *Lilly* and *Fiers* cases. Applicants' arguments are not found persuasive.

While it is acknowledged that the current claims differ from the *Lilly* and *Fiers* cases, as discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicants were in possession of the claimed genus. A representative number of species means that the species that are adequately described are representative of the entire genus. The specification discloses only a single representative species of the claimed genus, i.e., SEQ ID NO:2. Further, as stated above, there is substantial variation within the structure and/or function of the genus of claimed nucleic acids. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. At the time of the invention, one of skill in the art would recognize the absence of the ability to predict the function(s) of all species of claimed nucleic acids. For inventions in an unpredictable art, adequate written description of a genus that embraces widely variant species cannot be achieved by disclosing only one species within the genus. As described above, one of skill in the art would recognize that the claimed genus of variants encompass species having substantial variation of function within the genus and would recognize that the claimed genus of nucleic acids *comprising* only 20 or 60 nucleotides of SEQ ID NO:2 encompass species having substantial variation of structure and function within the genus. As such, neither the description of the structure and function of SEQ ID NO:2 nor the disclosure of solely structural features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus of claimed polypeptides.

2. The present claims define a genus which is highly variant.

Beginning at page 39 of Paper No. 7, applicants argue the claims do not recite a genus that is highly variant. Applicants argue that available evidence indicates that the claimed genus is of narrow scope. In support of applicants' assertion, they rely on the teachings of Brenner et al. (*Proc Natl Acad Sci*

USA 95:6073-6078, 1998). Applicants argue that, based on the teachings of Brenner et al., naturally-occurring molecules may exist that could be characterized as having phosphate transport activity with only 30% identity over 150 amino acid residues of SEQ ID NO:1. Applicants argue the claims recite a nucleic acid encoding a naturally-occurring amino acid sequence with at least 90% identity to SEQ ID NO:1, which has 401 amino acids. Applicants assert this variation is far less than those phosphate transporters having as little as 30% identity over at least 150 residues of SEQ ID NO:1.

As stated above, applicants improperly attempt to apply the teachings of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) to support their argument. Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) clearly state that their comparisons "have been assessed **using proteins whose relationships are known reliably from their [three dimensional] structures and functions**, as described in the SCOP database" (page 6073, abstract). In the instant case, the genus of claimed polynucleotides or polypeptides encoded by the claimed polynucleotides is related to SEQ ID NO:2 or 1, respectively, based solely on sequence – not on their three dimensional structures or their functions. Brenner et al. compare amino acid sequences of *functional* polypeptides encoded by genes at *different* loci and suggest that 30 % sequence identity between polypeptides having the aforementioned characteristics, i.e., functional polypeptides encoded by genes at different loci, can be used to propose functional similarity of the polypeptides. However, Brenner et al. clearly does *not* suggest that *all* amino acid sequences with at least 30 % identity over 150 amino acids to another amino acid sequence will share a similar function. Regarding prediction of an encoded polypeptide's function *based solely on nucleic acid sequence*, Brenner (*Trends in Genetics* 15:132-133) teaches that it is impossible to know the accuracy of functional assignment without empirical laboratory evidence (page 132, left column, second paragraph). Also, it is well known in the art that highly homologous proteins can have distinct functions. As supporting evidence, the examiner provides the reference of Scott et al. (*Nat Genet* 21:440-443) who teach a polypeptide that has 45 % sequence identity (it is noted that SEQ ID NO:1 similarly shares 48 % identity with NPT1) with a human sulfate transporter and that, based on structural homology has been proposed to function as a sulfate transporter (page 440, left column, abstract). However, an empirical analysis of

the protein measuring its ability to transport various ions revealed the protein is actually a chloride-iodide transport protein (page 441, left column, third full paragraph). Scott et al. "conclude that pendrin does not function as a sulfate transporter, as suggested by its close homology to other sulfate transporters, but instead functions as a sodium-independent transporter of chloride and iodide and state that their result shows the importance of confirming the function of a protein even when the protein shares significant homology to proteins of known function (emphasis added; page 441, left column, third full paragraph). Thus, a skilled artisan would recognize that 30% identity based solely on a primary amino acid sequence is *not* a reliable threshold for predicting function as asserted by applicants. It is noted that applicants' claims are drawn to nucleic acids encoding variants with at least 90% identity. As such, the examiner provides the reference of Seffernick et al. (*J Bacteriol* 183:2405-2410). Seffernick et al. teach a nucleic acid encoding a melamine deaminase (TriA). Seffernick et al. teach the nucleic acid encoding TriA shares 99% identity with a nucleic acid encoding an atrazine chlorohydrolase (page 2407, right column, middle), however, the encoded polypeptides catalyze distinct reactions and each does not utilize the others substrate (page 2405, abstract). While Seffernick et al. characterize their finding as "exceptional" (page 2409, left column, middle), this nonetheless provides evidence that polynucleotides, even those sharing significant identity, do not necessarily encode polypeptides having identical functions as asserted by applicants.

3. Advances in the state of the art from the time of *Lilly* and *Fiers* do not obviate adequate written description.

Applicants argue the state of the art at the time of the invention is further advanced than at the time of the *Lilly* and *Fiers* cases. Applicants argue the techniques and technological advances since the *Lilly* and *Fiers* up to the filing of the instant application in combination with the teachings provided in the instant specification are such that one of skill in the art would recognize that applicants were in possession of the claimed polypeptides. Applicants' arguments are not found persuasive. While advances in the art are undeniable and widely recognized, the point of the rejection is lack of written description and not lack of enabling disclosure. The state of the art still does not allow one of skill in the art to

predict the structure and function of naturally-occurring variants or nucleic acids comprising fragments of SEQ ID NO:2 based solely on a single disclosed polynucleotide structure – see for example, Seffernick et al. whose polynucleotides share 99% identity, share large sequence fragments, but have distinct functions. Most importantly, one skilled in the art would not be able to divine the functions of other naturally-occurring sequences or nucleic acids comprising fragments of SEQ ID NO:2 based on the knowledge of the function of only one disclosed species. For inventions in an unpredictable art, adequate written description of a genus that embraces widely variant species cannot be achieved by disclosing only one species within the genus. It is noted that the claims of the '740 patent of the *Lilly* case were limited by *both* structural and functional limitations (see for example claim 4 of '740), thus placing the artisan in possession of the attributes and features of all members of the claimed genus.

[11] The scope of enablement rejection of claims 3, 6, 7, 9, 12, 13, 46, 48, 57, and 58 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action (see item 11 of Paper No. 6). Applicants' arguments are summarized and rebutted as follows. For applicants' convenience, the examiner's rebuttal of applicants' arguments will maintain the format as used by applicants in Paper No. 7.

Beginning at page 41 of Paper No. 7, applicants argue that the polypeptide variants encoded by the nucleic acid of claim 3 are "naturally-occurring" and that through the process of natural selection, nature will have determined the "appropriate" amino acid sequences. Applicants argue it is routine experimentation to obtain those nucleic acids encoding the recited variants. Applicants argue that using the common nucleic acid isolation techniques of hybridization or PCR, a skilled artisan need not make and test vast numbers of nucleic acids, and instead need only use said techniques to identify those relevant variant-encoding polynucleotides that exist in nature. Applicants argue that, by extension, one of skill in the art could use fragments of variants of SEQ ID NO:2 as hybridization probes and optionally as arrays to detect full length polynucleotides. Applicants' arguments are not found persuasive. The claims encompass nucleic acids encoding variants and nucleic acids comprising fragments that have phosphate transport activity in addition to variant polypeptides that are non-functional or exhibit a function other

than phosphate transport activity. While techniques for isolation of nucleic acids encoding variants are known in the art, other than a method for screening those nucleic acids encoding polypeptides having phosphate transport activity, the specification provides no additional guidance in the form of assays for identifying those encoded proteins having activities other than phosphate transport. There are no working examples of variants of the SEQ ID NO:2 or nucleic acids encoding variants of SEQ ID NO:1. Furthermore, there is no guidance provided in the specification as to what *all* nucleic acids encoding variant polypeptides can be used for – particularly those variants encoding non-functional polypeptides.

Beginning at the bottom of page 42 of Paper No. 7, applicants argue the examiner's assertions that nucleic acid modifications may alter an encoded protein's function are based on the mere possibility that mutations can eliminate the activity of a naturally-occurring polypeptide. Applicants argue the examiner's assertions ignore the teachings of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) which speaks to the general applicability of using sequence homology to indicate protein homology and Bork (*Genome Res* 10:398-400) who teaches prediction of function by homology has a 90 % accuracy rate and all bioinformatics predictions have a 70% accuracy rate. Applicants' arguments are not found persuasive. It is noted that the claimed modified nucleic acids are not limited to those encoding naturally-occurring polypeptides. It is further noted that the reference of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) has not been presented for consideration by the examiner, therefore, the examiner would have had no opportunity to consider and allegedly ignore the teachings of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) prior to applicants' response to the Office action of Paper No. 6. Regarding the reference of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078), as stated above, Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) clearly state that their comparisons "have been assessed **using proteins whose relationships are known reliably from their [three dimensional] structures and functions**, as described in the SCOP database" (page 6073, abstract). In the instant case, the identity of the claimed variants is based solely on sequence identity – not on their three dimensional structures or their functions. Brenner et al. compare amino acid sequences of *functional* polypeptides encoded by genes at *different* loci and suggest that 30 % sequence identity between polypeptides having

the aforementioned characteristics, i.e., functional polypeptides encoded by genes at different loci, can be used to propose functional similarity of the polypeptides. However, Brenner et al. clearly does *not* suggest that *all* amino acid sequences with at least 30 % identity over 150 amino acids to another amino acid sequence will share a similar function. Instead, Brenner (*Trends in Genetics* 15:132-133) teaches that it is impossible to know the accuracy of functional assignment of a protein based solely on nucleic acid sequence without empirical laboratory evidence (page 132, left column, second paragraph). Regarding the reference of Bork (*Genome Res* 10:398-400), it is noted that applicants have ignored the teachings of Bork, particularly the footnote to Table 1 of Bork, which states that the evidence provided is a crude estimate and that "numbers in Table 1 are often overestimates because the test sets used are usually not representative of all sequences". It is noted that Bork does not elaborate on how low the accuracy may actually be. Addressing the examiner's assertions, the references of Broun et al. (*Science* 282:1315-1317) and Seffernick et al. (*J Bacteriol* 183:2405-2410) have been provided as supporting evidence of the unpredictability of making modifications to an encoding nucleic acid with an expectation of obtaining an encoded protein having a desired activity. The examiner's use of the term "modifications to an encoding nucleic acid, even minor modifications, **may** completely alter the function of the encoded protein" (emphasis added) emphasizes the unpredictability that the entire scope of claimed nucleic acids would encode polypeptides having phosphate transport activity, i.e., modifications **may or may not** alter the function of the encoded protein as there is a high degree of unpredictability in making mutations with an expectation that the encoded polypeptide will maintain a similar activity and the specification has provided no guidance as to those encoding nucleotides that are necessary (conserved) for encoding a protein having phosphate transport activity and those that are not.

Applicants argue (beginning at the bottom of page 42) the references of Broun et al. (*Science* 282:1315-1317) and Seffernick et al. (*J Bacteriol* 183:2405-2410) do not support the examiner's assertion that amino acid modifications can alter protein function. Addressing the Broun et al. reference, applicants argue the mutations as taught by Broun et al. do not completely alter the function of the desaturase to a hydroxylase as the mutant retains some desaturase activity. Applicants argue that Broun et al. note that

a small number of amino acid substitutions account for the functional divergence of a number of enzymes, and conclude from this remark by Broun et al. that this supports the notion that most amino acid substitutions have no effect or minimal effect on protein function. Applicants' arguments are not found persuasive. The examiner acknowledges the mutant desaturase of Broun et al. maintains desaturase activity. However, the desaturase of Broun et al., prior to mutation exhibited no hydroxylase activity – only upon mutation did the mutant desaturase of Broun et al. exhibit hydroxylase activity. While the four mutations of Broun et al. did not *completely* convert the desaturase activity to a hydroxylase activity, the mutations as taught by Broun et al. nonetheless led to the generation a novel activity for their desaturase, thus providing support for the unpredictability of modifying an encoding nucleic acid. The specification has provided no guidance as to those encoding nucleotides that are necessary (conserved) for encoding a protein having phosphate transport activity and those that are not or those encoding nucleotides that may be modified, resulting in the generation of a polypeptide having a novel, undesired, activity.

Addressing the reference of Seffernick et al., applicants argue the proteins having distinct functions as taught by Seffernick et al. belong to same enzyme superfamily. Applicants argue there is a member of this superfamily that catalyzes both deamination and dechloronation with triazine ring substrates. Applicants conclude from this that the 98% identity between the proteins of Seffernick et al. "correctly predicts their functional similarity and their membership in a common enzyme family". Applicants argue this example demonstrating the difficulty in predicting function does not contradict Bork et al. who allegedly teach that protein function is accurately predicted by sequence homology methods. Applicants argue in the Seffernick et al. example, sequence homology correctly assigns the proteins to a particular enzyme family whose members share similar enzyme activities. Applicants argue that Seffernick et al. do not contradict the evidence that one of skill in the art would reasonably conclude that NAPTR (SEQ ID NO:1) could be used in the same manner as the NPT1 phosphate transporter. Applicants' arguments are not found persuasive. While the enzymes of Seffernick et al. belong to the same superfamily, the enzymes nonetheless have distinct functions. It is noted that, in the instant rejection,

the reference of Seffernick et al. has been provided to support the unpredictability that the claimed variant nucleic acids will encode polypeptides having the identical function to SEQ ID NO:1 and not that SEQ ID NO:1 has an identical function to NPT1. Applicants' argument attempts to imply that the enzymes as taught by Seffernick et al. are functionally similar by belonging to the same superfamily of enzymes and is allegedly in line with the teachings of Bork. However, the enzymes are *not* functionally similar as evidenced by the title of the reference of Seffernick et al. – "Melamine Deaminase and Atrazine Chlorohydrolase: 98 Percent Identical but Functionally Diverse". Each of the enzymes – while being 99% identical at the encoding nucleic acid level - exhibits a distinct function and neither uses the other's substrate. This clearly contradicts the teachings of Bork. The mere inclusion of enzymes within a superfamily is not indicative of their functional similarity or divergence. One of skill in the art recognizes that homologous members of a superfamily may have diverse functions as evidenced by Gerlt et al. (*Genome Biol* 1:reviews0005.1-0005.10) teach that "even within homologous families of a single superfamily, the level of sequence similarity required for reliable prediction of function from sequence cannot be specified with confidence" (page 0005.2, right column, bottom to page 0005.3, left column, top). Gerlt et al. further teach their results "illustrate that mechanistic diversity does not require a large significant divergence in sequence, and underscore that high levels of sequence identity do not 'guarantee' the same enzymatic function" (page 0005.3, right column, middle), thus contradicting the teachings of Bork et al. and Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078). Collectively, the references of Broun et al., Seffernick et al., Brenner (*Trends in Genetics* 15:132-133), and Gerlt et al. provide evidence for the high degree of unpredictability that the claimed variants could be used in the same manner as the NPT1 phosphate transporter.

Applicants argue (beginning at page 44) that the teachings of Seffernick et al. who, applicants allege, recognizes that functional assignments based on >50 % sequence identity are considered to reasonably sound and that proteins with >98% sequence identity catalyzing different reactions is highly exceptional. Applicants allege that these statements by Seffernick et al. do not contradict the findings of Bork et al. who, applicants allege, teach that in general, sequence homology is an accurate method for

assigning biological function. Applicants' arguments are not found persuasive. It is noted that applicants' statement by Seffernick et al. regarding >50% sequence identity has been mischaracterized. In fact, Seffernick et al. teach their result of identifying two proteins with >98% identity and having distinct functions "underlies current genome annotation efforts where functional assignments based on >50 % sequence identity are considered to reasonably sound" (page 2409, left column, middle) and thus provides additional support for the uncertainty in assigning function based on structural identity alone. While it is acknowledged that Seffernick describe their findings as "highly exceptional", this reference nonetheless provides evidence for the unpredictability in assigning function to a variant based solely on sequence. Regarding the reference of Bork, it is noted that applicants have ignored the teachings of Bork, particularly the footnote to Table 1 of Bork, which states that the evidence provided is a crude estimate and that "numbers in Table 1 are often overestimates because the test sets used are usually not representative of all sequences". Furthermore, the state of the prior art suggests a high degree of unpredictability in assigning function based on sequence alone.

Applicants argue (beginning at page 44) the statement by Bork, that "predicting the function of a polypeptide... ...by sequence database searches has a considerable error rate" does not negate the "fact" that there is a 90% accuracy rate for the prediction of functional "features" by homology as disclosed by Bork. Applicants argue that, at most, that errors can occur in functional assignment. Applicants argue that Bork does not show that errors do not occur, but it allegedly quantifies the error rate at 10%. Applicants argue that the cited references do not contradict that such assignment methods are accurate more than not and, as such, one of skill in the art would reasonably conclude that NAPTR (SEQ ID NO:1) possesses the function of the family of phosphate transporter proteins. Applicants' arguments are not found persuasive. It is noted that the cited references used in the instant rejection have been applied to demonstrate the unpredictability of assigning function to the nucleic acid variants and nucleic acids comprising fragments as claimed and not to assigning function to the polypeptide of SEQ ID NO:1 as asserted by applicants. Regarding the reference of Bork, again it is noted that applicants have ignored the teachings of Bork, particularly the footnote to Table 1 of Bork, which states that the evidence

provided is a crude estimate and that "numbers in Table 1 are often overestimates because the test sets used are usually not representative of all sequences". Bork have not established a "fact" of 90% accuracy rate for the prediction of functional "features" by homology. One of the references Bork relies on in establishing this alleged "fact" is that of Brenner (*Trends in Genetics* 15:132-133). Brenner teaches an error rate of "at least 8% for the 340 genes annotated", provides evidence for why this error rate must be greater, and states, "the true error rate must be greater than these figures indicate". Thus, applicants characterization of the reference of Bork as statements of "fact" is misleading as Bork has not established a "fact". To the contrary, as evidenced by Broun et al., Seffernick et al., Brenner (*Trends in Genetics* 15:132-133), Gerlt et al., and Scott et al., the art recognizes the unpredictability in assigning function based on sequence identity alone.

Applicants argue the Office has failed to demonstrate that a skilled artisan could not make and use the claimed polynucleotides. Applicants argue the Office action has only provided isolated examples in which mutations can sometimes result in a shift of the biological activity of a polypeptide. Applicants argue the cited references have no bearing on the ability of a skilled artisan to make the relevant polynucleotides and their encoded polypeptides which already exist in nature, without undue experimentation. Applicants' arguments are not found persuasive. It is noted that the claims are not so limited to naturally-occurring nucleic acids or nucleic acids encoding naturally-occurring amino acid sequences. Instead, claims 13, 48, and 58 are drawn to polynucleotides *comprising* fragments of SEQ ID NO:2 or variants thereof – there is no limitation provided in these claims that the nucleic acids or encoded proteins be naturally-occurring. The Office action of Paper No. 6 has demonstrated that undue experimentation would be required for a skilled artisan to make and use the entire scope of claimed nucleic acids. The examiner has offered an analysis according to the Factors set forth in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)). The cited references of Broun et al., Seffernick et al., Brenner (*Trends in Genetics* 15:132-133), Gerlt et al., and Scott et al. provide the state of the prior art, which demonstrates the high degree of unpredictability that homologous proteins will share the same function and the high degree of unpredictability in making one or more mutations in an encoding nucleic

acid sequence with an expectation of obtaining an encoded protein having a desired biological activity. As the prior art is replete with examples of mutations altering the function of a protein, the examiner has selected the cited references as representative and are not "isolated examples" as asserted by applicants.

Applicants argue (beginning at page 45 of Paper No. 7) the Office action has not provided arguments directed to the enablement of arrays comprising nucleic acids hybridizable with at least 30 contiguous nucleotides of a polynucleotide comprising SEQ ID NO:2. Applicants argue a skilled artisan could make and use the arrays without undue experimentation, provided the specification and the state of the art and provide examples in support thereof. Applicants' arguments are not found persuasive. Applicants' argument appears to be directed to claim 48. It is noted that the nucleic acid of the array of claim 48 is not so limited to a nucleic acid hybridizable with at least 30 contiguous nucleotides of a polynucleotide comprising SEQ ID NO:2. Instead, as stated in a previous Office action (see item 11 of Paper No. 6) the claim is so broad as to encompass an array comprising *all* nucleic acid molecules comprising a first oligonucleotide or polynucleotide that specifically hybridizes with at least 30 contiguous nucleotides of a target polynucleotide of claim 12, which itself is so broad as to encompass variants having at least 90% identity to SEQ ID NO:2. The examiner has stated the scope of claim 48 is not commensurate in scope with the enablement provided by the specification. However, the examiner acknowledges that the arguments set forth in Paper No. 6 were not specifically directed to the array of claim 48. In order to clarify the record, the examiner has provided an analysis of those Factors most relevant to the instant rejection – including the array of claim 48 - below.

Applicants argue (beginning at page 45 of Paper No. 7) the Office action has provided no arguments concerning the lack of enablement of polynucleotides comprising fragments of SEQ ID NO:2. Applicants argue a skilled artisan could make and use the claimed fragments without undue experimentation, provided the specification and the state of the art and provide examples in support thereof. Applicants argue that, contrary to the standard set forth in *In re Marzocchi* (169 USPQ 367, 369 (CCPA 1971)), the Office action has failed to provide reasons why one would doubt that the guidance provided by the specification would enable a skilled artisan to make and use the claimed polynucleotides

comprising fragments of SEQ ID NO:2 or arrays comprising nucleic acids hybridizable to portions of the recited polynucleotides. Applicants conclude that a *prima facie* case for non-enablement has not been established for the clamed nucleic acids. Applicants' arguments are not found persuasive. It appears that applicants have ignored the examiner's arguments directed to nucleic acids comprising fragments of SEQ ID NO:2 (see item 11 of Paper No. 6). It is noted that the function of the nucleic acids comprising fragments of SEQ ID NO:2 is not limited to a hybridization probe and, from the specification, it appears that an intended use of the claimed nucleic acids is for protein expression (see for example, page 14, lines 19-21, and page 41, lines 7-19 of the instant specification). While the examiner has clearly provided reasons as to why the disclosure fails to enable the entire scope of nucleic acids comprising fragments of SEQ ID NO:2 and variants thereof as encompassed by the claims (see item 11 of Paper No. 6), in order to clarify the record, the examiner has provided an analysis of those Factors most relevant to the instant rejection – including the claimed nucleic acids comprising fragments of SEQ ID NO:2 and variants thereof - below.

It is the examiner's position that the claimed nucleic acids and array would require undue experimentation for a skilled artisan to make and/or use. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). In order to reiterate the examiner's position, those Factors most relevant to the instant rejection are addressed below.

- The breadth of the claims: the claims are so broad as to encompass *all* polynucleotides encoding a polypeptide comprising a naturally-occurring amino acid sequence that is at least 90 % identical to SEQ ID NO:1 (claim 3), *all* polynucleotides comprising a naturally-occurring polynucleotide that is at least 90 % identical to SEQ ID NO:2, complements thereof, and RNA equivalents thereof, respectively (claim 12), *all* polynucleotides comprising at least 20 or 60 contiguous nucleotides of: nucleotides 1183-1454 of SEQ

ID NO:2 or a complement thereof, a naturally-occurring polynucleotide that is at least 90 % identical to nucleotides 1183-1454 of SEQ ID NO:2 or a complement thereof, and RNA equivalents thereof (claims 13 and 58), an array comprising *all* nucleic acid molecules comprising a first oligonucleotide or polynucleotide that specifically hybridizes with at least 30 contiguous nucleotides of a target polynucleotide of claim 12 (claim 48), and *all* polynucleotides comprising a naturally-occurring polynucleotide that is at least 95 % identical to SEQ ID NO:2, complements thereof, and RNA equivalents thereof, respectively (claim 57). The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claims. In this case, the disclosure is enabling only for SEQ ID NO:2 and an array comprising SEQ ID NO:2.

- The lack of guidance and working examples: the specification provides a single working example of the broad scope of claimed nucleic acids as described above, i.e., SEQ ID NO:2 encoding the phosphate transport protein of SEQ ID NO:1. Regarding claim 3(b), 12(b), (d), and (e), 46, 57(b), (d), and (e), and 58(b), (d), and (e), the specification fails to provide guidance for how to use the entire scope of claimed nucleic acids, which encompass variants having *any* function. Regarding claims 13(a) and (c), 46, 48, and 58(a) and (c), the specification fails to provide guidance for how to make *and* use the entire scope of claimed nucleic acids, which encompass variants and fragments having *any* function and almost any structure. The specification provides guidance only for making and using the nucleic acid of SEQ ID NO:2 for encoding the polypeptide of SEQ ID NO:1. It is noted that it appears from the specification that an intended use of the claimed polynucleotides is for protein expression (see for example, page 14, lines 19-21, and page 41, lines 7-19 of the instant specification). The specification fails to provide guidance regarding those nucleotides of SEQ ID NO:2 that may be modified by substitution, insertion, or deletion and maintain phosphate transport activity. The specification fails to provide guidance regarding those regions or fragments of SEQ ID NO:2 that are necessary for phosphate transport activity and which of those fragments may be elongated with additional nucleotides and maintain phosphate transport activity. Regarding the array of claim 48, which depends from claim 12(b),

the specification fails to provide guidance as to which 30 nucleotides of a variant of SEQ ID NO:2 are useful for identifying nucleic acids encoding SEQ ID NO:1. The specification provides no guidance regarding those nucleotides of SEQ ID NO:2 that are conserved within the family of phosphate transport proteins. The specification provides only a single working example of a nucleic acid for use as a hybridization probe, i.e., SEQ ID NO:2 (see page 40, Example VI of the instant specification). Thus, the specification provides insufficient guidance to enable the entire scope of the claimed nucleic acids and array.

- The unpredictability of the art and the state of the art: a nucleic acid sequence determines an encoded proteins' structural and functional properties or the identity of a nucleic acid which will hybridize thereto. Predictability of which changes in a polynucleotide can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity (in this case sodium-dependent transport of phosphate or the ability to hybridize to a phosphate transport-encoding nucleic acid) requires a knowledge of and guidance with regard to which nucleotides of the encoding sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. In this case, such guidance has not been provided. Furthermore, the positions within an encoding nucleic acid's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide with the desired activity/utility are limited and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given encoded protein to diminish with each further and additional modification, e.g. multiple substitutions. The prior art teaches that two polypeptides encoded by naturally-occurring polynucleotides, while sharing significant sequence homology, may have completely different functions. As a representative example, Seffernick et al. (*J Bacteriol* 183:2405-2410) teach that, while a melamine deaminase and atrazine chlorohydrolase differ at only 9 amino acids out of 475 and share 99% nucleic acid identity and greater than 98% amino acid identity, the two enzymes catalyze completely different reactions, i.e., deamination and dechloronation, and neither enzyme utilizes the other's substrate. Alternatively, just as sequences sharing sequence

identity may not have similar function, sequences with no sequence identity may share similar function. For example, Tenenhouse et al. (*Am J Physiol* 275:F527-F534) teach that proteins, Glvr-1 and Ram-1, share no sequence similarity to NPT1, yet have phosphate transport activity (page F528, left column, top). Thus, there is a high degree of unpredictability in assigning function to a polypeptide based on sequence identity as recognized by the state of the art.

- The amount of experimentation required: While recombinant and mutagenesis techniques and hybridization screening techniques are known, it is not routine in the art to screen for multiple nucleotide substitutions or multiple modifications, as encompassed by the instant claims. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the instant case, the specification should provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. The specification fails to provide such guidance. Therefore, in view of the broad scope of the claimed nucleic acids and array, the lack of guidance provided by the specification, the unpredictability of the art supported by the state of the art, an undue amount of experimentation would be required for a skilled artisan to make and/or use the claimed nucleic acids and array.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including all nucleic acids and the array as described above. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

[12] The rejection of claims 3, 13, and 58 under 35 U.S.C. 102(a) as being anticipated by Gasparini (IDS reference 18 of Paper No. 1; GenBank Accession Number Z83593) is withdrawn in view of applicants' amendment.

Double Patenting

[13] The rejection of claims 3-7, 9, 10, 12, and 57 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,985,604 is maintained. Applicants' request for the requirement for submission of a Terminal Disclaimer be held in abeyance until there is an indication of allowable subject matter is acknowledged.

Conclusion

[14] All claims are rejected. No claim is in condition for allowance.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

Rebecca Prouty

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1600~~
1605

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OM nucleic - nucleic search, using sw model

Run on:         March 11, 2003, 10:39:25 ; Search time 0.001 Seconds
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Searched:       1 seqs, 272 residues

Total number of hits satisfying chosen parameters:      2

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      and is derived by analysis of the total score distribution.

                                    SUMMARIES

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                                    ALIGNMENTS


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us-09-991-212a-5

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